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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,519	10/23/2000	Robert Joseph Isfort	8311	9641

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 11/30/2001

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/694,519	ISFORT ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-14, 16(in part), 18-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 16 (in part), 17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group X in Paper No. 8 is acknowledged. The traversal is on the ground(s) that

- Inventions outlined in Groups I-XXIV are so closely interrelated that in order to preserve unity all the groups should be prosecuted in the same application, because they all "involve the regulation of the vasoactive intestinal peptides".
- "The major reason for restriction requirements is the unduly burdensome effect in searching the art for variety of species. In this instance, although the Examiner has noted twenty-two groups, only four classes for searching have been cited by the Examiner. .... Class 435, Subclasses 6, 7.1 and 7.2, Class 514, Subclasses 1 and 44, Class 424, Subclass 130 and Class 530, Subclass 387.1".
- The claims are directed to methods of identifying compounds and methods of their use. The Applicants quote from *In re Ochiai* , which holds that a compound and a method or process of using those compounds are the same invention and argue that separating the prosecution of compounds from the methods of their use by restriction is improper.

This is not found persuasive because:

- The restriction requirement is based on the fact that the different groups are different inventions, not species, and they are patentably distinct. Methods of identifying candidate compounds and methods of using these compounds are different inventions. In addition, methods of identifying potentially therapeutic compounds *in vitro* and *in vivo* are patentably distinct, as are methods of treatment using different

classes of compounds (proteins, DNA, etc). For example, a method of treating muscular atrophy by administering a receptor agonist is different from the method of treatment involving overexpression of the receptor by gene therapy or regulation of the receptor signaling pathway.

- The reason for the lack of differences in classification of these methods lies in the fact that current classification system didn't keep up with the proliferation of compounds and methods in the biotechnology area. The searches for prior art involve mostly database (patents and publications) searches, rather than searches of particular classes and subclasses, because the latter do not provide the full picture of the prior art available.

The requirement is still deemed proper and is therefore made FINAL.

2. Considering the last point, only Group IX (claim 15, drawn to a pharmaceutical composition comprising a safe and effective amount of a VPAC receptor agonist) and Group XXIV (claims 24-26, drawn to a purified antibody specific for the VPAC receptor) are product claims. Claim 15 and the new claim 27, drawn to a method of increasing skeletal muscle mass or function in a subject comprising administering to the subject a safe and effective amount of a compound that acts through the VPAC receptor are combined with the elected Group X.

3. Claims 1-14, 16 (in part which does not pertain to the VPAC agonist), 18-26 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups I-VIII and XI-XXIV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently

named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure legend for Figures 3A and 3B lists X-axis labels as A-G (page 9, lines 7-11), whereas the Figure itself has the X-axis labels 1-7. Correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 15-17 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VPAC (vasoactive intestinal peptide) receptor agonists specific for either $VPAC_1$ ($[K^{15}, R^{16}, L^{27}$, VIP(1-7), GRF(8-27)-NH_2]), $VPAC_2$ (Ro 25-1553) or both (PACAP-38), pituitary adenylate cyclase-activating polypeptide) receptors, does not reasonably provide enablement for any other compound or any of the other agonists listed in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide any indications that VPAC receptor agonists such as VIP (vasoactive intestinal peptide), PACAP-27, helodermin, peptide histidine isoleucine amide (PHI), peptide histidine methionine amide (PMI), peptide histidine valine amide (PVI), growth hormone releasing hormone (GHRH, GRH, GRF), secretin, glucagon, (Arg15, Arg21) VIP, [Arg 15,20,21,

Leu17]-VIP-Gly-Lys-Arg-NH_2, multimeric VIP fusion protein, Ro-1392, PACAP(6-38) when administered to a subject would result in an increase of the skeletal muscle mass or function.

The agonists of VPAC receptors listed above are related to VIP, whose receptors are widely distributed in the central and peripheral nervous system and in plasma membranes of many organs and tissues (gastrointestinal tract, lung, heart, uterus, adrenal, adipocytes, enterocytes, hepatocytes, liver, etc.). VIP has a broad range of biological actions, such as vasodilation of vessels, brochodilation, relaxation of various muscles (esophageal sphincter, fundic muscle, gallbladder smooth muscle, colonic smooth muscle of the intestines), glycogenolysis and lipolysis, bone resorption, release of insulin, glucagon, or somatostatin in the pancreas, stimulation of prolactin, growth hormone (GH) release in the pituitary, etc. (Said, J. Endocrinol. Invest., vol. 9, p. 191-200, 1986).

In addition, helodermin, glucagon, GRF, secretin have their own specific receptors, but also bind to the VIP receptors. For example, secretin, GRF, PHI and helodermin bind to the VIP receptor, VIP, GRF, PHI and helodermin bind to the secretin receptors (in pancreas and exocrine cells), glucagon binds to its receptors in the liver, and GRF to its receptors in the pituitary gland (Laburthe et al., Ann. NY Acad. Sci., vol. 527, pp. 296-313, 1988, see Fig. 9). GRF and PHI were found to be VIP receptor agonists (Emami et al., Peptides, vol. 7, pp. 121-127, 1986, see Abstract), and PHM was found to be a VIP agonist with low potency on human VIP receptors (Laburthe et al., Life Sci., vol. 36, pp. 991-995, see Abstract).

PACAP-38 and PACAP-27 in addition to binding to their own receptors bind to the VIP receptors (Ulrich et al., Gastroenterology, vol. 114, pp. 382-397, 1998, see page 387, third paragraph).

Therefore, taking all of the above facts into account, administration of any of the above VPAC agonists, despite the fact that they are related, cannot be predicted to have an effect of increasing muscle strength or function, and may potentially lead to harmful outcome, as they also target other receptors. As noted by Musso et al. (U.S. Patent No. 4,835, 252): " ...the naturally occurring VIP has so many biological activities that its use is limited, because beneficial effects are associated unavoidably with significant, deletorious side effects, especially when the VIP is administered intravenously..." (col. 2, lines 27-31).

Due to the large quantity of experimentation necessary to establish whether the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 would result in an increase of muscle mass or function, the lack of direction/guidance presented in the specification regarding administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 resulting in an increase of muscle mass or function, the lack of working examples directed to the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 and resulting increase of muscle mass or function, the complex nature of the invention (agonist binding to several receptor types), the unpredictability of the effects of the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 on an increase of muscle mass or function (see discussion above), undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15-17 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 15 is indefinite because of the limitation "safe and effective amount of a VPAC receptor agonist". It is unclear what is encompassed by the terms "safe and effective".

B) Claims 16, 17 and 27 are indefinite because of the limitation "safe and effective amount of a compound". It is unclear what is encompassed by the terms "safe and effective".

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Gourlet et al. (WO 98/02453).

Gourlet et al. teach peptides which are highly selective for the VIP1 (=$VPAC_1$) receptor, are agonists or antagonists, and pharmaceutical compositions comprising the peptides and pharmaceutically acceptable carrier (page 4, lines 8-11; page 5, lines 14-29; page 9, lines 17-24).

12. Claims 16, 17 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Vittone et al. (Metabolism, vol. 46, pp. 89-96, 1997).

Vittone et al. teach improved muscle function in elderly men (who suffer from the decrease in muscle mass and strength due to age-related decrease in growth hormone, GH, and

insulin-like growth factor-I, IGF-I) after administration of single nightly injections of GHRH (Abstract; page 94, paragraph 4).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
November 27, 2001

Kenneth R. Horlick, Ph.D
KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP 1800
11/28/01